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RESEARCH ARTICLE

Comparative Study on Precision and Interference of Maltose and Vitamin C among three Glucometers Commonly Used in United Arab Emirates (U.A.E)

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Abstract:

Aim:

To evaluate the suitability of commercially available glucometers in the UAE in terms of accurate and reliable blood glucose measurements.

Background:

Portable glucometers are employed for measuring blood glucose levels, offering distinct advantages such as providing instant results and being user-friendly when compared to laboratory reference analyzers. However, certain molecules, such as those found in medications, can interfere with the accuracy of glucometer readings.

Objective:

To evaluate the precision and interference in the presence of maltose and vitamin C of three glucometers commercially available in the UAE.

Methods:

We utilized plasma samples to conduct two types of experiments: a precision experiment and an interference experiment. We compared the precision of three glucometer brands available in the United Arab Emirates [Accu-Chek Instant™, One Touch Select Plus Flex™, and Trister GlucoScan™] in the presence or not of various interfering molecules, such as Maltose and Ascorbic Acid (Vitamin C).

Results:

Accu-Chek Instant™ demonstrated the highest precision among the glucometers tested, with a coefficient of variation of less than 5% for all measured glucose values. In contrast, OneTouch Select Plus Flex™ and Trister Glucoscan™ exhibited higher variability in precision, with coefficients of variation of 11.4% and 11%, respectively. Accu-Chek Instant™ consistently performed well in terms of bias and precision in the presence of interferences, and does not display glucose readings above 50mg/dL of Vitamin C. Notably, Ascorbic acid induced a greater bias compared to Maltose for all three glucometers.

Conclusion:

The performance of the glucometer is affected by its testing methodology. Accu-Chek Instant™ shows improved precision and is able to detect the presence of Vitamin C. When it comes to Maltose interference, it results in a higher bias change but lower variability, which can be addressed by applying a correction factor.

Keywords: Accuracy, Precision, Glucometers, Interference, United Arab Emirates, Maltose, Ascorbic Acid.

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1. INTRODUCTION

Diabetes mellitus, a primary heterogeneous metabolic disorder characterized by chronic hyperglycemia, is often linked to impaired insulin function or production [1]. This disease poses a global challenge, contributing significantly to

Mortality, morbidity, and disability rates. Managing diabetes is complex, requiring not only glycemic control but also specific risk reduction strategies [2].

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The rapid growth of the global population has led to a surge in diabetes cases, with projections indicating that the worldwide prevalence across all age groups may reach 4.4% by 2030, affecting approximately 366 million individuals [3].

Regionally, in 2011, the prevalence of diabetes in the United Arab Emirates (UAE) stood at 18.8%, ranking it 10th in the world. Projections suggest that by 2030, diabetes prevalence in the UAE could rise to 21.6% [4]. According to the report from "Diabetes Atlas 2021", the global diabetes prevalence is 10%. In the United Arab Emirates (UAE), the diabetes prevalence for 20–79-year-olds is 12.3%, and the age-adjusted comparative diabetes prevalence is cited at 16.4%. It is estimated that $2,109.5 would be the diabetes-related expenditure per diabetic person [5].

These statistics underscore the urgency for researchers to conduct studies related to diabetes. The country is grappling with a serious diabetes epidemic that affects all its residents, necessitating research to understand how glucometers function when confronted with various interferences. This research also sheds light on factors that can elevate blood sugar readings and helps identify potential risk factors.

The UAE's culturally diverse population presents additional challenges, as different dietary patterns can impact diabetes monitoring and management practices. Therefore, educating patients about food components that interfere with blood sugar measurements is crucial for better health management and overall well-being.

Self-Monitoring of Blood Glucose (SMBG) using portable glucose monitoring devices is crucial for managing diabetes cases [6]. SMBG is necessary multiple times a day, such as before meals, before exercise, at bedtime, and during various daily activities for individuals on insulin pump therapy or multiple-dose insulin regimens [2].

The American Diabetes Association (ADA) recommends that patients using insulin injections or insulin pump therapy should perform SMBG three or more times daily. Portable glucometers serve as viable alternatives to the reference glucose analyzers found in laboratories. Additionally, the ADA accepts portable glucometer readings as valid if they are within 5% of the reference analyzer measurements [7]. The Food and Drug Administration (FDA) recommends that 95% of SMBG results are within +/- 15% of the reference and 99% of the results are +/-20% of the reference [8]. The ISO 15197:2003 standards dictate that 95% of the measurements must be +/- 15 mg/dL for concentrations below 75mg/dL, and +/- 20mg/dL for concentrations above 75mg/dL [9].

The presence of limitations in terms of accuracy and precision in Self-Monitoring of Blood Glucose (SMBG) can lead to errors in the care of diabetes patients. One tragic instance involved the overdose of insulin in patients on peritoneal dialysis due to the misinterpretation of high maltose levels as high glucose levels. This misinterpretation occurred because some glucometers, particularly those based on glucose dehydrogenase pyrroloquinoline quinone, cannot distinguish between maltose and glucose [10].

Outliers are not uncommon with point-of-care (POC) glucometers. Results that deviate by 20% above or below the true glucose level are considered outliers, and the occurrence of such outliers can potentially harm patients [10].

Errors in SMBG can arise from various sources, including incorrect technique, concurrent medical conditions, and interfering substances. Failing to wash hands before testing can lead to a "pre-analytical error", resulting in higher glucose readings, while not drying them can yield lower glucose readings due to "hemodilution" Some interfering substances can produce false and potentially fatal results. For instance, in patients with anemia, glucose levels may appear inflated, prompting the use of "intra-arterial glucose measurements' for ICU patients and in operating rooms".

This inflation can also manifest in different conditions, depending on the type of meter used [10]. It can also be influenced by factors such as non-calibration, hematocrit levels, edema, vasodepressor medications, and body temperature [11].

Glucometers are typically designed based on either spectroscopic or electrochemical methods, with the latter being more commonly used due to lower errors in comparison to spectroscopic methods. These methods are categorized based on the enzymes and co-enzymes employed for measurement, including the glucose oxidase (GOx) method [most frequently used], glucose dehydrogenase-based pyrroloquinoline quinone (GDH-PQQ) method, glucose dehydrogenase-based nicotin-amide adenine dinucleotide (GDH-NAD) method, and glucose dehydrogenase-based flavin adenine dinucleotide (GDH-FAD) method [12]. Different glucometers utilize different enzymes, but they can all be susceptible to interference from the same substances (Heinemann, 2010). Inaccuracies in glucose measurements can result from various factors, including physical, patient-related, or pharmacological factors [13].

The extent of interference strongly depends on the glucometer's mechanism, and not all glucometers are affected by the same substances. The table from reference [14] shown below, demonstrates interference with different systems (Table **1**).

Table 1. Interference in different mechanisms due to ascorbic acid and maltose [14].

Interference	GDH-FAD	GDH-NAD	GDH-PQQ	GOD-FAD
Ascorbic acid	No	No	No *	Yes
Maltose	No	No	Yes	No

Note: *only Accuchek™ is exception to the following table, but Accuchek™ compact BG shows interference above 3mg/dL.

There are three main types of enzymes responsible for interacting with glucose measurements. The hexokinase method, commonly used in laboratories, relies on spectrophotometry. In contrast, both glucose oxidase (GOx) and glucose-1-dehydrogenase (GDH) enzymes are utilized in glucose biosensors for SMBG [15]. In the hexokinase method, glucose and ATP are oxidized by hexokinase to form glucose-6-phosphate, which is further oxidized by NAD to produce NADH. The concentration of NADH is quantified using spectrophotometry at 340nm [16].

Glucose Oxidase (GOx) is considered the standard biosensor enzyme due to its relatively high selectivity for

glucose compared to other enzymes. It offers several advantages, including availability, cost-efficiency, and the ability to function under a wide range of pH levels, temperatures, and ionic strengths. The concept of a glucose biosensor revolves around GOx catalyzing β-D-glucose with molecular oxygen, resulting in the production of hydrogen peroxide and gluconic acid

$$\text{Glucose} + \text{GOx} - \text{FAD} \longrightarrow \text{Gluconolactone} + \text{GOx} - \text{FADH}_2 \quad \textbf{(1)}$$

$$\text{GOx}-\text{FADH}_2+\text{O}_2 \longrightarrow \text{GOx}-\text{FAD}+\text{H}_2\text{O}_2 \quad \textbf{(2)}$$

$$\text{H}_2\text{O}_2 \longrightarrow 2H^+ + O_2 + 2e \quad \textbf{(3)}$$

For GOx to work as a catalyst, it requires a redox cofactor called flavin adenine dinucleotide (FAD). In reaction {1}, FAD is reduced to $FADH_2$, becoming the first electron acceptor. Reaction {2} shows $FADH_2$ reacting with oxygen to regenerate the cofactor, producing hydrogen peroxide. At the catalytic anode, typically made of platinum, hydrogen peroxide undergoes oxidation as shown in reaction {3} consequently, the number of electrons transferred is easily detected by the electrode, with the flow of electrons being proportional to the concentration of glucose molecules in the blood [15].

Glucose-1-Dehydrogenase (GDH) is a unique enzyme suitable for amperometric glucose sensing and is readily available in test strips. It operates effectively at lower applied potentials and remains unaffected by oxygen concentrations [17]. Dissolved oxygen (O_2) does not impact the reaction of the GDH enzyme. Unlike the GDH-PQQ enzyme system, which has a rapid electron transfer rate and high effectiveness, GDH generates NADH [nicotinamide-adenine dinucleotide] when NAD+ acts as a cofactor. NADH plays a crucial role in the glucose oxidation process [15].

Maltose (Fig. **1**) can lead to elevated glucose measurement results. Maltose, or maltodextrin, is a polysaccharide that can be absorbed, especially in cases of gastric inflammation. Normally, it is further broken down into monosaccharides before absorption. In diabetic patients who use peritoneal dialysis fluid, maltose is produced as one of the metabolites of icodextrin, resulting in spikes in glucose measurements. This interference may also occur when patients receive therapies containing maltose. This elevation is consistently observed in GDH-PQQ analyzers as well as in GOx glucometers [18]. Maltose interferes with methods based on GDH-PQQ, as the metabolism of icodextrin generates a saccharide chain containing a reducing glucose group at the end, which reacts with the test and produces higher readings [19].

Many medications, such as those prescribed for viral infections, chronic fatigue syndrome, and cancer, contain significant amounts of Ascorbic Acid (Vitamin C) [20]. Medications with high concentrations of vitamin C can disrupt the accuracy of glucometers. This interference arises from the structural similarity between Vitamin C (Fig. **2a**) and Glucose (Fig. **2b**), which can lead to incorrect readings of elevated blood glucose levels and a significant oversight of hypoglycemia [21].

Moreover, high levels of ascorbic acid are recognized as significant contributors to fatal hyperglycemia and hypoglycemia. In the case of electrochemical-based glucose biosensors, the oxidation of ascorbic acid on the electrode surface results in the generation of more electrons and a higher current. Elevated concentrations of ascorbic acid (vitamin C) can lead to a noticeable increase in glucose levels due to varying degrees of interference with glucose biosensors. These variations may arise from differences in test strips, technical methodologies, or the enzymes used [15].

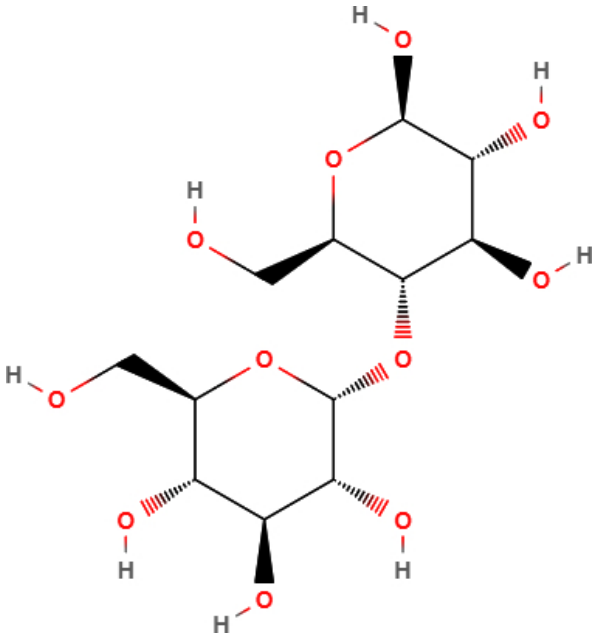

Fig. (1). Maltose structure.

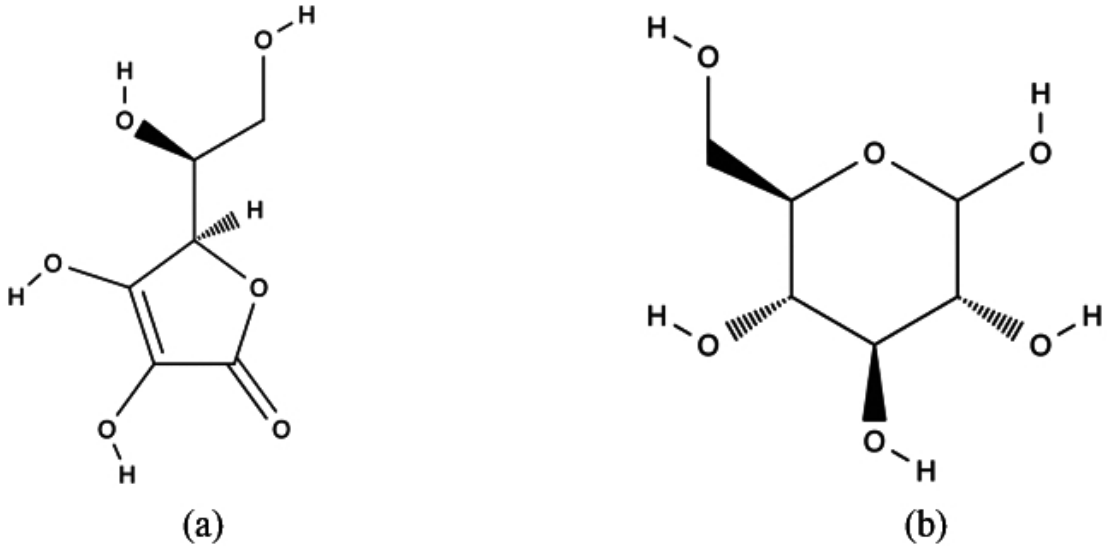

Fig. (2). Molecular structures of (**a**) ascorbic acid (vitamin C) and (**b**) glucose.

In the context of the United Arab Emirates (UAE), there appears to be limited research conducted, to the best of our knowledge, on assessing the precision and interference factors associated with locally available glucometers. Notably, one study conducted in the UAE addressed the interference of vitamin C with HbA1c testing [22]. Given the economic advantages of portable glucometers and the significance of understanding glucometer performance, it is essential to provide educational resources to the Emirati community for selecting the most suitable glucometer. Considering the substantial percentage of the UAE population affected by diabetes, addressing this gap in the literature is imperative to meet the needs of the increasing number of individuals living with diabetes.

The objective of this study is to evaluate the precision and interference of glucometers readily available in the United Arab Emirates, such as Accu-Chek Instant®, One Touch Select Plus Flex®, and Trister GlucoScan®, in the presence of interfering molecules Maltose and Ascorbic Acid. For instance, if a patient is known to have elevated levels of interferents in their blood, the findings from this analysis can be instrumental in making necessary corrections or selecting the most appropriate glucometer, one that is least affected or unaffected by the presence of interfering molecules.

2. MATERIALS AND METHODS

2.1. Samples Collection

After obtaining ethical approval, we collected 9 venous non-fasting blood samples, with each sample totaling 5 mL in volume. These samples were gathered using SST tubes (Serum-separating tubes) from a pool of 3 healthy participants. To ensure the reliability of our study and minimize potential interferences, we excluded individuals with metabolic diseases, those infected with hepatitis B or C, HIV-positive individuals, individuals with anemia, those receiving treatment for anemia or iron deficiency, individuals who had donated blood within the last month, and pregnant individuals. The blood donors were recruited from among the research participants, and the blood withdrawal procedure was carried out by skilled laboratory technicians in the clinic's laboratory department.

2.2. Instrumentation

The glucose concentration of the blood samples was determined *via* two methods. Initially, the baseline glucose content in the blood samples was measured using the Abott Anality C analyzer in the clinic laboratory. Subsequently, we employed the most commonly available glucometers from the UAE market. Specifically, we selected three glucometers: Accu-Chek Instant™, One Touch Select Plus Flex™, and Trister GlucoScan™. This experiment was conducted at the Department of Chemical Engineering of the College of

Engineering at Abu Dhabi University (ADU), United Arab Emirates (Table **2**).

2.3. Interferences and variables

We tested various concentrations of Ascorbic acid (Vitamin C) and Maltose at different blood glucose levels as shown in Table **3**. In the precision study, we introduced varying concentrations of dextrose. All the chemical compounds used in these experiments were obtained from King Mariot Medical Equipment.

Table 2. STAR method- key resources table.

Reagent or Resource	Source	Identifier
Biological samples	-	-
Healthy adults blood	Advanced Cure Diagnostic Center	N/A
Healthy adults plasma	Advanced Cure Diagnostic Center	N/A

(Table 2) contd.....

Reagent or Resource	Source	Identifier
Chemicals, peptides, and recombinant proteins		
Dextrose	King Mariot Medical Equipment	CAS: 50-99-7
Ascorbic Acid (Vitamin C)	King Mariot Medical Equipment	CAS: 50-81-7
Maltose	King Mariot Medical Equipment	CAS: 6363-53-7
Critical commercial assays		
Trister GlucosScan Blood Glucose Monitoring System	Dareen Pharmacies LLC	LOT: BAF105
Accu-Chek Instant Blood Glucose Monitoring System	Dareen Pharmacies LLC	REF: 07819374
OneTouch Select Plus Flex Blood Glucose Monitoring System	New Pharmacy W L L	SN: [21]GCPTTHZS
Accu-Chek Instant Test Strips	Dareen Pharmacies LLC	REF: 07819382446
Trister GlucoScan Test Strips	Dareen Pharmacies LLC	REF: PS004-INT
OneTouch Select Plus Flex Test Strips	New Pharmacy W L L	REF: AW 06966804A
Deposited data		
Raw and analyzed data	This paper	Available upon request
Software and algorithms		
Inkscape	Software Freedom Conservancy	https://inkscape.org/release/inkscape-1.2.2/
Other		
Polyscience Water Bath	Preston Industries, Inc.	SN: W41791458

Table 3. Interferences concentration setup.

Interferences	Number of Aliquots	Concentration Range
Maltose	6	10, 40, 200, 480, 600, and 800 mg/dL
Ascorbic Acid (Vitamin C)	6	5, 10, 25, 50, 100, and 200 mg/dL

2.4. Blood Pools Preparation

A total of 9 Serum-separating tubes (SST) samples were collected and combined, resulting in a total blood volume of 45 mL. We prepared three different blood glucose samples (pools) representing critical hyperglycemia (low), hyperglycemia (normal), and critical hypoglycemia (high) without the addition of any concentrated glucose solutions or interfering factors [20].

The low blood glucose pool was created by allowing 30 mL of blood to sit at room temperature for 24 hours. This extended period leads to enhanced glycolysis and a significant reduction in blood glucose levels [23].

To prepare the normal blood glucose pool, we centrifuged 15 mL of blood. For the high blood glucose pool, we adjusted its glucose concentration by spiking it with a glucose solution (Dextrose) at various concentrations, including 60, 120, and 420 mg/dL.

Each blood pool underwent centrifugation at 4,000 RPM for 10 minutes to separate the plasma. The normal pool yielded 8.25 mL of plasma, which was promptly analyzed to establish its baseline value. The samples were then stored in a blood freezer at 3°C. Subsequently, 16.5 mL of plasma with low glucose levels was collected and analyzed in the same manner on the following day.

2.5. Precision Study

Approximately 3 mL of plasma from the low blood pool was utilized for the precision study. This sample was then divided into two parts: a baseline sample and three separate aliquots, each containing 0.792 mL (792 uL). These aliquots were subsequently spiked with the desired concentrations of dextrose, specifically 60, 120, and 420 mg/dL. To calculate the dextrose stock solution concentrations (C_3), we employed the formula $C_2=(C_3V_3-C_1V_1)/V_2$.

2.6. Interference Study

The highest concentration stock solutions for Maltose and Vitamin C were prepared by dissolving the specified amount in 100 mL of deionized water [20]. We created six different targeted concentrations as shown in Table **3** for each interference using the serial dilution method.

To aid dissolution, a Polyscience water bath was used to create stock solutions for vitamin C (at 25°C) and maltose (at 70°C).

The interferences were introduced into the plasma of both the normal and low blood pools. The samples are spiked with interference at 1% sample volume.

3. RESULTS

The precision of the three glucometers was evaluated over a span of three days, with five repetitions for each glucose level. To assess the data from the precision experiment, the Coefficient of Variation (CV%) was used to measure the deviation from the mean, and the average bias% was used to assess the deviation from the baseline glucose value in the plasma. While not necessary for precision assessment, the average bias% was considered to provide additional insights.

The CV% for AccuChek™ in within-run precision for all glucose levels consistently remained within 5% across all three days, as evident in the bar graphs shown in Fig. (**3a**, **b**, and **c**).

Trister™ GlucoScan displayed the highest CV% in most runs, except for 120 mg/dL and 420 mg/dL on day 3 (Fig. **3c**) and 120 mg/dL on day 2 (Fig. **3b**). A general observation from Fig. (**3a**, **b**, and **c**) is that the CV% decreases as the glucose level in the plasma increases, ranging from a maximum of 11.4% CV at 47 mg/dL to 3.6% CV at 420 mg/dL on day 3. The lower precision is particularly noticeable at glucose levels of 47 and 89 mg/dL, especially for Trister™.

When observing the between-run precision (Fig. **3d**), which represents the cumulative result of within-run precision studies, it becomes evident that the CV% for AccuChek™ consistently remains below 5% for all tested glucose levels, complying with ADA standards. In contrast, the CV% reaches a maximum of 11% for Trister™ and 11.4% for OneTouch™.

Overall, it is observed that the variation in CV% is higher for between-run precision compared to within run precision. For a more detailed insight into the variation of the dextrose values, please refer to Figs. (**S1** and **S2**) in Supplementary Material.

The average bias% of the Trister™ glucometer, observed across different glucose levels in the plasma pool, is the highest, ranging from 6% to 59%, followed by OneTouch™, which ranges from 7% to 23%. AccuChek™ shows the least average bias and is the only glucometer to exhibit both positive and negative bias, ranging from -6% to 5%. For additional data, please refer to Table **S1** in Supplementary Material.

3.1. Interference

3.1.1. Maltose

Glucose readings were collected in triplicate for each glucometer across various maltose concentrations, including 10, 40, 200, 480, 600, and 800 mg/dL. These readings were examined in both the low glucose plasma pool (47 mg/dL) and the normal plasma pool (89 mg/dL). To assess interference, p-values obtained from correlation tests and 95% confidence intervals were utilized to detect correlations between maltose concentration and glucose readings. The average bias% was examined to understand the deviation of glucose readings from the baseline glucose, while the Coefficient of Variation (CV%) was used to determine the variability in the collected data.

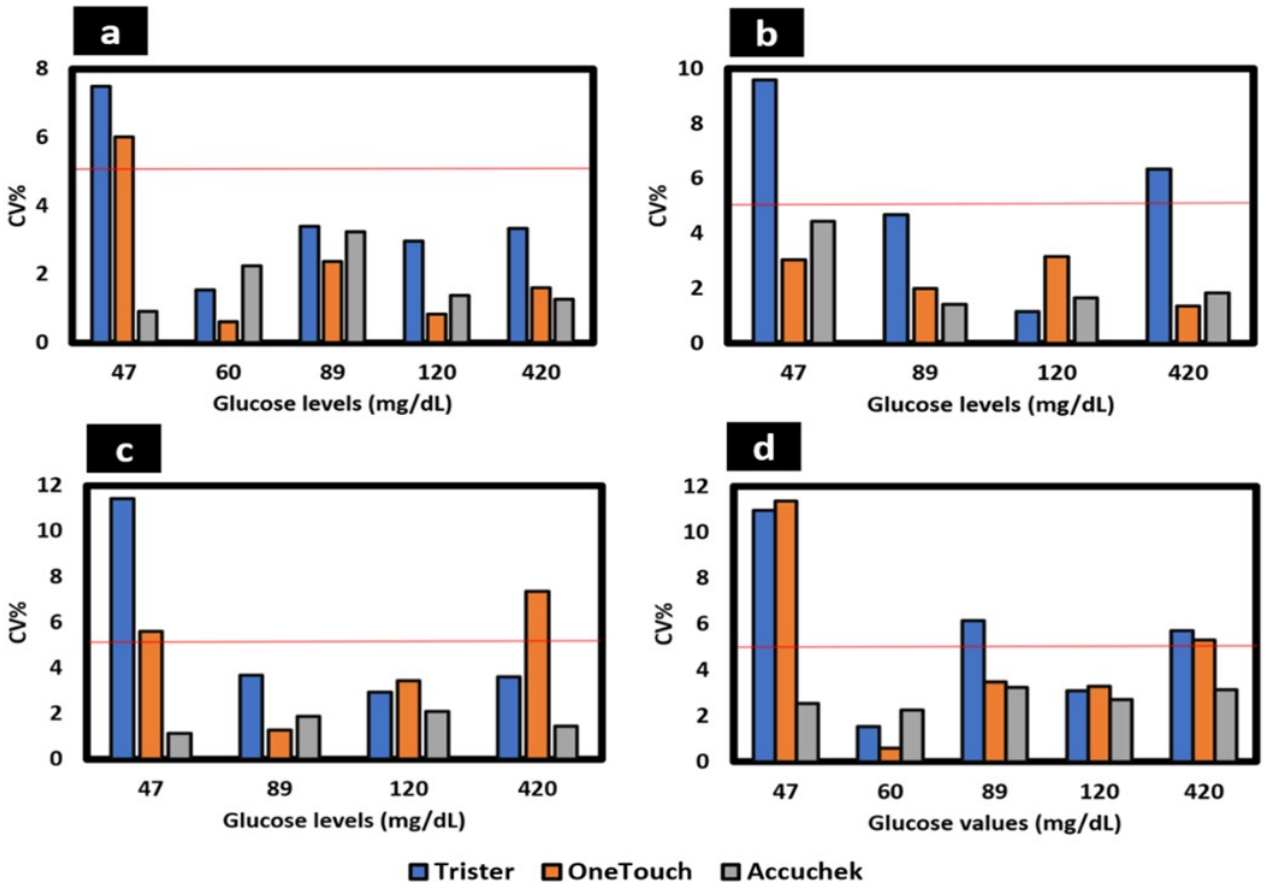

Fig. (3). Plots of coefficient of variat ion (CV%) for Trister™, OneTouch™ and Accuchek™ over 3 days for varying dext rose levels.
a) CV% against glucose levels of 47,60,89,120& 420mg/dL for within run precision on day 1.
b) CV% against glucose levels of 47,89,120& 420mg/dL for within run precision on day 2.
c) CV% against glucose levels of 47,89,120& 420mg/dL for within run precision on day 3.
d) CV% against glucose levels of 47,60,89,120 and 420mg/dL for all 3 days of measurement (between run precision).
*Within run precision encompasses 5 trials done for each glucose level and each glucometer, between run precision over 3 days is for 15 trials for each glucose level for each glucometer. For 60mg/dL glucose level in plasma, the data is recorded on day 1 only.

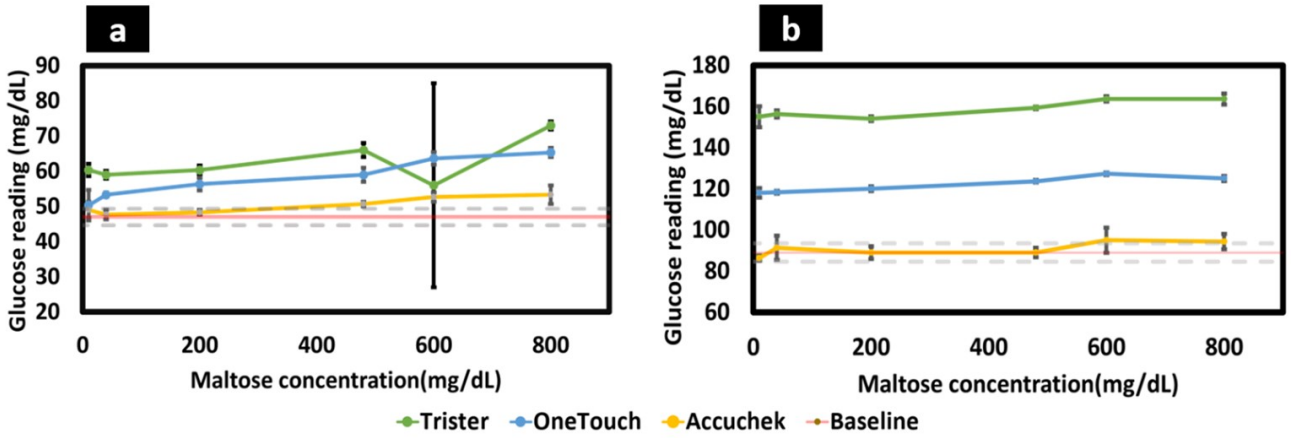

Fig. (4). Glucometer readings *versus* maltose concentrations of 10,40,200,480,600&800mg/dL.
a) Glucose readings for different concentrations of maltose for 47 mg/dL glucose in plasma.
(*Note: at 600 mg/dL, the error bars for Trister™ are relatively large due to presence of outlier).
b) Glucose readings for different concentrations of maltose for 89mg/dL glucose in plasma.

Maltose exhibits a positive correlation in all three glucometers, with the most significant impact on the change in average bias observed in AccuChek™, followed by OneTouch™ and Trister™.

Three trials were conducted at each interferent concentration. The Fig. (**4a**, **b**), display the error bars that represent 95% confidence intervals, and the average value of glucose readings are plotted on the y-axis. From Fig. (**4a**, **b**), it is evident that there is a slight increasing trend in all three glucometers.

P-values obtained from correlation tests were used to determine if the average values of glucometer readings from the three trials were associated with varying maltose concentrations. It was observed that the p-values varied depending on the blood glucose level of the pool for the same interferent concentration and glucometer.

OneTouch™ displayed p-values of <0.001 and 0.008 for low and normal pools, respectively. For AccuChek™, a p-value of 0.09 for the normal blood pool was observed along with considerable overlap in confidence intervals. Conversely, for the low blood pool, AccuChek™ yielded a very low p-value of 0.004.

Trister™ exhibited the opposite trend of AccuChek™ by showing a possible correlation at the high glucose plasma pool.

In general, it can be said that, upon observing confidence intervals (Table **S4a-b**), there is a significant overlap for all the glucometers in both low and high blood pools, making it less certain to assert a positive correlation. Hence, the possibility of a positive correlation exists, with potential prevalence in OneTouch™ for both low and normal blood pools, AccuChek™ for the low plasma pool, and Trister™ for the normal plasma pool. Additional data on p-values can be found in Table **S3a** in supplementary material.

The relative change in average bias was calculated by comparing the maximum average bias observed in the glucose readings for varying interferent concentrations (Table **S2a**) with the average bias from the precision experiment, which involved varying dextrose levels only. It is noteworthy that AccuChek™ exhibited the highest change in % average bias, with a value of 9.7, compared to only -0.2 for Trister™ in the 47 mg/dL plasma pools. A similar trend was observed in the 89 mg/dL plasma pool, with the change being 4.4 for AccuChek™ and 0.1 for Trister™. Therefore, it can be concluded that the highest relative change in bias occurred for AccuChek™, followed by OneTouch™. Additional data can be found in Table **S2b** in supplementary material.

Regarding the variability of collected glucometer readings at each interferent concentration, AccuChek™ demonstrated less variability in both low and normal glucose levels compared to Trister™ and OneTouch ™, which exhibited higher variability at low glucose levels in plasma (Table **S6a**, **b**).

3.1.2. Vitamin C

The interference of vitamin C was tested across vitamin C concentrations of 0, 10, 25, 50, 100, and 200 mg/dL. Three trials were conducted for each glucometer at every vitamin C concentration in the plasma pools. Similar to the maltose interference study in the previous section, correlation tests, confidence intervals, average bias%, and CV% were used to assess this interference.

From Fig. (**5a**) (for the low glucose pool at 47 mg/dL) and Fig. (**5b**) (for the normal pool at 89 mg/dL), a strong positive trend was observed. AccuChek™ displayed error E12 at and above 50 mg/dL of vitamin C for both low and normal glucose pools.

When performing correlation tests, it was found that AccuChek™ showed a p-value of 0.059 for the low blood pool, and the null hypothesis was not rejected. However, for the normal blood pool, the p-value was 0.03, indicating statistical significance. Upon observing the confidence intervals (Table **S5a-b**), it was noted that the intervals were mostly distinct and did not overlap for all glucometers. An interesting observation was the slight trough in the confidence interval at the 10 mg/dL concentration of vitamin C for all glucometers, except for Trister™ and OneTouch™ at the low plasma pool (Table **S5a**, **b**).

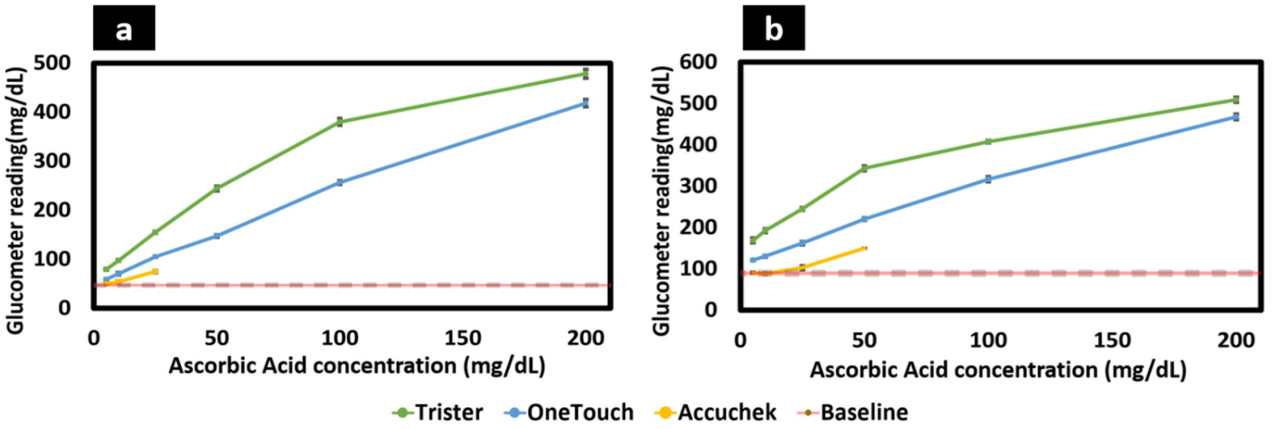

Fig. (5). Glucometer readings *versus* Ascorbic Acid concentrations of 10, 40, 200, 480, 600 &800mg/dL.
a) glucose readings for different concentrations of vitamin C for 47 mg/dL glucose in plasma. (*Note: at 600 mg/dL, the error bars for Trister are relatively large due to presence of outlier).
b) glucose readings for different concentrations of vitamin C for 89mg/dL glucose in plasma.
3 trials were done at every ascorbic acid concentration, and the average value of glucose reading is plotted in y-axis for both a) and b). The error bars represent 95% confidence intervals.

The relative change in the average bias% was highest for OneTouch™ [23], followed by Trister™ and AccuChek^{C} [12] at a plasma glucose level of 47 mg/dL (low pool). A similar trend was observed for the normal glucose pool (Table **S2b**). Therefore, in terms of bias, OneTouch™ and AccuChek™ were more affected than Trister™. It is also noteworthy that the precision of all three glucometers, at all concentrations in the presence of vitamin C, was less than 5% (Table **S6c-d**), which is evident from the 95% confidence interval error bars in Fig. (**5a - b**).

4. DISCUSSION

In terms of precision, AccuChek™ Instant shows consistent performance across all glucose levels and complies with the ADA standard of a 5% coefficient of variation (CV). In contrast, OneTouch™ and Trister™ do not meet the 5% CV protocol. One possible reason for the precision of AccuChek™ could be that it measures glucose levels directly in the plasma, even though fresh capillary blood is applied to the meter. This mechanism aligns with the International Federation of Clinical Chemistry and Laboratory Medicine standards, but such details are not found in the manuals for OneTouch™ and Trister™. These details about the mechanism are mentioned in the AccuChek™ user manual #07819374. OneTouch™ also shows consistent performance, except at low glucose levels where the CV% is relatively high. It uses the glucose oxidase mechanism, as mentioned in the OneTouch™ Select plus Flex owner's manual (registered number: ER41149/15). According to the user manual for Trister™ GlucoScan test strips (model no. TS377BG), the glucometer may yield incorrect measurements if the sample used is not whole blood, which may explain the high deviation from the baseline glucose measurements.

In a study evaluating the accuracy and precision of glucometers used in Sri Lanka, it was found that most glucometers did not comply with the less than 5% CV recommended by ADA, as used in other papers. However, one glucometer, the brand of which is not mentioned, did meet this standard [24]. Another study conducted on five glucometers in Saudi Arabia also reported CV% in the range of 38-41%, far from the 5% recommendation, with AccuChek™ having the lowest CV% and Freestyle Optium Neo having the highest [25]. AccuChek™ (Performa) performed better in precision studies conducted in New Zealand on low and high control solutions compared to Optium Xceed 5 seconds and 10 seconds meters [26].

In this study, AccuChek™ uses the GDH-FAD (Glucose dehydrogenase with Flavin Adenine Dinucleotide coenzyme) mechanism, while Trister™ and OneTouch™ both utilize the GOx (Glucose oxidase) mechanism. GOx is known as the most commonly used mechanism in glucose sensing. It functions by oxidizing glucose and reducing oxygen in the air into hydrogen peroxide, which is then oxidized or reduced on the glucometer electrode. To address the issue of oxygen concentration in the air interfering with glucose readings, GDH mechanisms were introduced as they are less sensitive to oxygen. These mechanisms may differ in the coenzymes they use. The PQQ coenzyme is known for its "low substrate specificity" [27]. GDH-FAD is cited as attractive for glucose sensing because it is oxygen-independent and specific. Hence, it can be expected that GDH-FAD should perform better than GOx mechanism-based glucometers, and the study's results in this regard are discussed below.

Regarding interference, it is expected that Glucose oxidase (GOx) based meters are more substrate-specific and should not interfere with sugars other than glucose. Glucose Dehydrogenase with Flavin adenine dinucleotide coenzyme (GDH-FAD) based meters only react with the sugar xylose, apart from glucose [28]. However, in this study, it is observed that even GOx meters are impacted by maltose, although to a lesser degree when compared to vitamin C. This is evident when Figs. (**4** and **5**) are compared. It can also be said that the degree of positive correlation between maltose concentration and glucose readings is not very strong. Nevertheless, it does have a significant impact on bias, demonstrating interference.

A study by [19] reaffirms that GDH-based meters are interfered with by maltose and also mentions the independence of GOx-based meters from being affected by maltose. In contrast, another study by [18] cites the occurrence of maltose interference in a GOx-based meter.

A possible explanation for interference in this study with Glucose oxidase meters may be the use of distilled water to create maltose stock solutions. The presence of a weak acid or weak base can initiate hydrolysis of maltose into glucose molecules since the solvent used is water, which may not have an exact pH of 7. This could be due to slight heating to 70°C to achieve maltose dissolution when creating stock solutions for the interference experiments or due to the pH of the plasma. However, it is evident that maltose creates a higher average bias in the GDH-FAD-based AccuChek™ compared to the GOx-based Trister™ and OneTouch™, indicating that GOx-based meters are more sugar-specific than GDH. Since the results indicate that AccuChek™ shows lower variability in bias and a more consistent coefficient of variation %, a correction factor can be used to account for bias and make it suitable for clinical use. It is more advantageous to use a correction factor in a meter that provides more precise values even in the presence of interference, as the correction factor is more likely to be a constant. This lower variability in GDH-based meters is expected as [27] mentions how GOx meters are easily affected by oxygen levels.

In the case of vitamin C, interference is observed in both GDH and GOx mechanisms in this study. This is supported by a strong positive correlation between Vitamin C concentration and glucose values, as indicated by distinct 95% confidence intervals and low p-values found from the correlation test. Only AccuChek™ Instant suppresses glucose readings above 50mg/dL of glucose, but a positive correlation is still observed up to a 25mg/dL concentration of vitamin C. Therefore, both GOx-based Trister and OneTouch™, as well as GDH-based Accu-Chek, are affected.

A study by [29] found that both GDH-based Roche AccuChek inform II and Abbott Precision Xceed Pro were interfered with by Vitamin C concentrations. The Nova StatStrip, based on Glucose oxidase, does not display glucose readings when Vitamin C is detected, similar to the Accu-Chek glucometer in this study, thus preventing incorrect patient treatment. The Vitamin C molecule undergoes oxidation at the electrode, producing current that can lead to incorrect readings [29]. Other studies also support the fact that both glucose oxidase and dehydrogenase are affected, as AccuChek Advantage (GOx-based) and AccuChek Advantage H (GDH-based) are both affected by ascorbic acid [23]. Therefore, the results of our study align with other works in the literature as discussed above.

Another point to consider is the use of plasma in this study instead of whole blood. The water concentrations differ in plasma and in the blood's cellular components, with the hematocrit percentage influencing the water content in blood. The increased water content in plasma causes a glucose concentration greater than that of whole blood by about 11-12%. This can significantly affect the bias% of the glucometers, and it's something to take into account when interpreting the results from the experiments in this study, as they were conducted on plasma and not whole blood [30]. It's worth noting that AccuChek™ user manual #07819374 mentions the use of glucose measurements from plasma directly. One possible explanation is provided in reference [30], which mentions that some meters provide glucose readings after the separation of the cellular portion from the plasma and display readings from the plasma, which can be corrected using the hematocrit level of the patient.

CONCLUSION

The glucometer's mechanism significantly impacts precision and performance in the presence of interferences. AccuChek™ is the most precise among the three tested glucometers, consistently demonstrating a Coefficient of Variation (CV%) of less than 5% across varying dextrose concentrations. It operates on the GDH-FAD mechanism, unlike Trister™ and OneTouch™, which use the GOx mechanism. Accu-Chek™ also performs well in the presence of Vitamin C (Ascorbic acid).

Accu-Chek™ exhibits a notable change in average bias for Maltose but maintains overall better precision with a CV% below 5% and lower variability in bias. Therefore, it can be used for patients exposed to maltose, along with a suitable correction factor to account for bias. As a result, AccuChek™ is the recommended glucometer based on this study. It offers precision, accurately monitors ascorbic acid levels above 50mg/dL to prevent misleading glucose measurements, and maintains precision in the presence of maltose when a correction factor is applied.

However, it's important to note some limitations of this study. Plasma from centrifuged intravenous blood samples was used instead of the typical fingerstick blood used for glucose readings. The stock solutions for maltose and vitamin C were prepared directly in distilled water as the solvent, and the impact of this choice on the experiment is unclear. The use of SST tubes for blood withdrawal may also have introduced variables into the results. The experiments were conducted over 5 days, and residual cellular components from the blood could have led to glycolysis, altering glucose values. This was observed in the precision experiment at 60mg/dL glucose, which is why days 2 and 3 were excluded from the precision study.

Future studies could consider replicating these experiments using whole blood instead of plasma and include a broader range of locally available glucometers. Additionally, research on non-invasive glucometer devices that do not require finger-pricking would be valuable, as new technologies continue to emerge. Investigating interference on fresh capillary blood, varying hematocrit levels, and other external factors could provide further insights. Exploring the simultaneous impact of two interferences and potential interactions between them would also be worthwhile. Finally, analyzing the assay method in terms of cost-effectiveness and identifying cost-effective meters for global benefit could be a valuable avenue of research.

AUTHORS CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

ADA	=	American Diabetes Association
BG	=	Blood Glucose
CV	=	Coefficient of variation
FADH2	=	Flavin Adenine Dinucleotide
GOx	=	Glucose oxidase
GDH-FAD	=	Glucose-Dehydrogenase-Flavin-Adenin-Dinucleotide
GDH-NAD	=	Glucose dehydrogenase- nicotinamide adenine dinucleotide
GDH-PQQ	=	Glucose dehydrogenase pyrroloquinoline quinone
HbA1c	=	Hemoglobin A1c
ICU	=	Intensive care unit
ISO	=	International Organization for Standardization
POC	=	Point of Care
RPM	=	Revolutions per minute
SMBG	=	Self-Monitoring of Blood Glucose
SST	=	Serum-separating tube

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Bioethics (IRB) committee at Abu Dhabi University, UAE provided ethical approval for this study (File number: COE-22-10-00035).

HUMAN AND ANIMAL RIGHTS

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

A consent form has been signed for blood collection for a laboratory protocol and participation in this study

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available in the Zenodo Repository at https://zenodo.org/records, reference number [13825952]. Further information and resource requests should be directed to and fulfilled by the student lead contact, [S.A].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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